USE OF BORATE-POLYOL COMPLEXES IN OPHTHALMIC COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 09/597,310, filed Jun. 20, 2000, (now U.S. Pat. No. 6,365,636), which is a continuation of U.S. patent application Ser. No. 09/109,453, filed Jul. 2, 1998, (now U.S. Pat. No. 6,143,799), which is a divisional of U.S. patent application Ser. No. 08/479,281, filed Jun. 7, 1995, (now U.S. Pat. No. 5,811,466), which is a divisional of U.S. patent application Ser. No. 08/198,427, filed Feb. 22, 1994, (now U.S. Pat. No. 5,505,953), which is a continuation-in-part of U.S. patent application Ser. No. 08/118,833, filed Sep. 7, 1993, (now U.S. Pat. No. 5,342,620), which is a continuation of U.S. patent application Ser. No. 07/879,435, filed May 6, 1992, (now abandoned).

BACKGROUND OF THE INVENTION

This invention relates to the use of borate-polyol complexes in ophthalmic compositions. In particular, these complexes are useful as buffers and/or antimicrobial agents in aqueous ophthalmic compositions, including those ophthalmic compositions containing polyvinyl alcohol.

Ophthalmic compositions are generally formulated to have a pH between about 4.0 and 8.0. To achieve a pH in this range and to maintain the pH for optimal stability during the shelf life of the composition, a buffer is often included. Borate is the buffer of choice for use in ophthalmic compositions, since it has some inherent antimicrobial activity and often enhances the activity of antimicrobials; however, when polyvinyl alcohol (PVA) is also an ingredient in the composition, borate and PVA form a water-insoluble complex which precipitates out of solution and acts as an irritant in the eye. This incompatibility of borate and PVA in contact lens solutions is well-known, and has been discussed, for example, in an article by P. L. Rakow in *Contact Lens Forum*, (June 1988), pages 41–46. Moreover, borate buffer cannot be effectively used below pH 7.0 due to its low buffering capacity to lower pH.

Since borate is incompatible with PVA, ophthalmic compositions containing PVA are generally buffered with acetate, phosphate or other buffers. There are disadvantages to using these alternative buffers: for example, acetate is a weak buffer (pK_a of about 4.5), so a relatively large amount is needed; on the other hand, phosphate is a good buffer but, when used in concentrations generally found in ophthalmic formulations, it reduces the antimicrobial activity of preservatives.

It is well known that small organic compounds, such as benzalkonium chloride (BAC), chlorhexidine, thimerosal have excellent antimicrobial activity; however, it is now known that these small organic antimicrobials are often toxic to the sensitive tissues of the eye and can accumulate in contact lenses, particularly soft, hydrophilic contact lenses. More recently, polymeric antimicrobials such as Polyquad® (polyquaternium-1) and Dymed® (polyhexamethylene biguanide) have been used in contact lens care products as disinfectants and preservatives. While these polymeric antimicrobials exhibit a broad spectrum of antimicrobial activity, they generally have relatively weak antifungal activity, especially against *Aspergillus niger* and *Aspergillus fumigatus*.

A need therefore exists for ophthalmic compositions which have an optimal pH for stability and efficacy, but whose antimicrobial efficacy is not compromised.

SUMMARY OF THE INVENTION

This invention provides such ophthalmic compositions. The ophthalmic compositions of the present invention comprise borate-polyol complexes which have surprisingly been found to have increased antimicrobial activity as compared to boric acid or its salts, particularly with respect to organisms such as *A. niger*. Moreover, these complexes unexpectedly increase the antimicrobial efficacy of other antimicrobial agents when used in combination.

The borate-polyol complexes are formed by mixing boric acid and/or its salts with polyols, such as mannitol, glycerin or propylene glycol, in an aqueous solution. The resultant solution may then be used as a buffer and/or antimicrobial agent in aqueous ophthalmic compositions, even where such compositions also contain PVA. The borate-polyol complexes of the present invention are also useful in unpreserved saline solutions.

The borate-polyol complexes of the present invention are particularly useful as adjunctive disinfecting agents in contact lens disinfecting solutions containing monomeric quaternary ammonium compounds (e.g., benzalkonium chloride) or biguanides (e.g., chlorhexidine) or polymeric antimicrobials, such as polymeric quaternary ammonium compounds (e.g., Polyquad®, Alcon Laboratories, Inc., Fort Worth, Tex.) or polymeric biguanides (e.g., Dymed®, Bausch & Lomb, Rochester, N.Y.).

The compositions of the present invention may optionally contain PVA; such compositions are particularly useful in contact lens care products which are targeted for wearers of rigid gas-permeable contact lenses (RGPs), who often complain of discomfort. PVA is a viscosity enhancer and is used extensively in all types of RGP products in order to improve the comfort and wearing time of RGPs. PVA is also extensively used as a viscosity enhancer for pharmaceutical ophthalmic compositions such as eye drops, gels or ocular inserts.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "borate" shall refer to boric acid, salts of boric acid and other pharmaceutically acceptable borates, or combinations thereof. Most suitable are: boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts.

As used herein, and unless otherwise indicated, the term "polyol" shall refer to any compound having at least two adjacent -OH groups which are not in trans configuration relative to each other. The polyols can be linear or circular, substituted or unsubstituted, or mixtures thereof, so long as